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| 09/783,487 | 02/14/2001 | Tito Andrew Serafini | 10239-010 | 7095 |

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PENNIE AND EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 100362711

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| EXAMINER |
| WOITACH, JOSEPH T |

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| ART UNIT | PAPER NUMBER |
| 1632 | 10 |

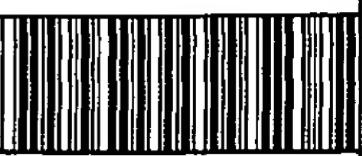
DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

| | |
|-------------------------------|-----------------------------|
| Application No. 09/783,487 | Applicant(s) Seafini, T. |
| Examiner Joseph Woitach | Art Unit 1632 |



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on Sep 23, 2002

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-158 is/are pending in the application.

4a) Of the above, claim(s) 28-31 and 61-158 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-27 and 32-60 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. _____.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

| | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1632

DETAILED ACTION

This is an original application, filed February 14, 2001.

Election/Restriction

Applicant's election with traverse of in Paper No. 11. is acknowledged. The traversal is on the ground(s) that Groups I and III and Groups II and IV should be rejoined because in each case the methods necessarily produce the products. See Applicants response pages 3-4.

Applicants arguments are found persuasive in part because while Examiner maintains that the inventions of each of the groups are distinct because other methods could be used to generate the products as set forth in the restriction requirement (paper number 8, bridging pages 3-4).

Examiner agrees that the method would necessarily produce the product and that it would not be an undue burden to search and examine the products and the methods to produce said products.

The requirement is still deemed proper and is therefore made FINAL.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1-158 are pending. Claims 28-31 and 61-158 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being

Art Unit: 1632

no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No 11. Claims 1-27 and 32-60 are currently under examination.

Information Disclosure Statement

The information disclosure statement filed July 23, 2002, paper number 9, indicates that a copy of each of the references cited was submitted with the IDS, thus it complies with 37 CFR 1.98(a)(2). However, a copy of each of the references is not present in the file. It has been placed in the application file, but the information referred to therein has not been considered. Examiner apologizes for any convenience this may cause Applicants, and requests a duplicate copy of the references for review.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see for example page 22, lines 6, 10, 19 and 27. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

Art Unit: 1632

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 and 32-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Art Unit: 1632

The basis of the rejection focuses on the ability to provide a regulatory sequence of a characterizing gene which provides for expression that is substantially the same as the expression pattern as the endogenous gene. It is noted that the specification lists numerous genes whose endogenous expression has been characterized. However, the specification does not teach the specific promoter sequences for each of these genes, nor does it provide evidence for the ability of the promoters outside the context of the endogenous genome to function or provide an expression pattern which is the same as the endogenous promoter. In particular, dependent claims recite specific biological pathways (claim 17) and specific physiological conditions (claim 21) in which the transgenes must be expressed, however the specification fails to provide the necessary teaching to affect the specific expression pattern or the genes to express to affect the specific conditions. It is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Further, case law teaches (*Ex parte Forman*, 230 USPQ 546,547 (BPAI 1986)) that “the disclosure of a patent application must enable practice of the invention claimed without undue experimentation”, wherein factors involved in the determination of undue experimentation were deemed to include “the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims.” In the instant case, the behavior of transgenes is unpredictable and

Art Unit: 1632

requires a reduction to practice for proof of concept. Thus, the specification fails to provide the necessary guidance to provide for the promoters or affect the specific phenotypes encompassed by the claims.

The prior art teaches that even if one can isolate a promoter region of a given gene, often aspects of regulation can not be determined. For example, Eid *et al.* (Dev. Dyn, 1993) teach that transgenic mice generated with various Hoxb-6 gene promoters operatively linked to a LacZ reporter gene could not reproduce the regulation of the endogenous Hoxb-6 gene (see summary in Table 1, page 210 and summary in abstract, page 205). A more current example by Sun *et al.* (Biochem Soc, 2002) teach the characterization of the prosaposin gene in transgenic mice. First, even among specific constructs, the level of expression and pattern of expression was shown to vary among the several lines generated (page 10). In comparing the marker gene expression and the endogenous prosaposin gene, Leinwand *et al.* conclude a generalized expression pattern could be generated, however additional elements of the promoter fragment appear to be necessary (see summary in abstract). Additionally, the present specification teaches that various homologue or orthologue promoters can be used in the invention, however the art teaches that even the same promoter from different species do not share the same function or expression pattern. For example, Thomas *et al.* (Exp. Cell Res, 2000) teach that the regulation of the osteocalcin from the mouse and human have divergent expression controls. Thomas *et al.* generate a transgenic mouse with the human OC promoter operatively linked to a CAT reporter, and comparing the expression of the reporter gene and the endogenous osteocalcin gene differed

Art Unit: 1632

in response to acute (OH)₂D₃ treatment (page 399, bottom of second column). Further, a more general response to PTH appeared to be related to treatments and choice of lines used (page 399, second column) concluding that the regulation of the human and mouse promoters differs in many aspects (page 400, top of second column and summarized in abstract). The behavior of the transgene can even be affected on how it is delivered. For example, Linney *et al.* teach that transgene expression in zebrafish can be affected by the means used to deliver the transgene. Specifically, comparing direct injection and the use of retrovirus delivery Linney *et al.* describe that the GFP marker gene varied temporally and expression levels varied among the transgenics made (see summary in Table 1 and Figure 4). In *Genentech, Inc. v Novo Nordisk a/S*, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the assertion of providing a promoter that provides the required expression pattern cannot be considered a minor detail which can be omitted in the process of providing an enabling disclosure.

Art Unit: 1632

The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). With respect to transgene behavior and to the ability to affect expression of a particular transgene to produce a particular phenotype this particularly true and true in the art of transgenics. Without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The observation is further supported by Mullins *et al.* (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins *et al.* state that "a given construct may react very differently from one species to another." See page S39, Summary. Wall *et al.* further report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." See page 2215, first paragraph. Since the applicants have not disclosed the nucleic acids encompassed by the claims, there is no way to predict efficiency nor expression of a transgene. Further, because the specification does not disclose an expected effect of introducing the nucleic acid, nor if/what cellular material it expects to modify, the claims encompass changes which may produce an animal which is not viable or incapable of producing progeny. Additionally, it is noted that dependent claims recite specific pathways and specific phenotypes with which characterizing genes are associated, however the specification fails to provide any teaching of any of these

Art Unit: 1632

specific genes in any pathway or genes which are responsible for producing any of the specific phenotypes. The specification provides no specific description or details of these genes or a means to isolate and providing these genes within the context of the claims. Finally, the use of an IRES sequence for multiple transgene expression does not necessarily provide for controlled or regulated expression. Jankowsky *et al.* (Biomol Eng, 2001) teach that despite high copy number, bi-cistronic transgene expression in the CNS of transgenic mouse lines produced different expression patterns than those demonstrated by lines in which two separate transgenes were used (see summary in abstract).

The specific methods taught and relied upon to generate transgenic animals in the instant specification are those generally known in the art, and fully enabled for the insertion of a polynucleotide into an animal of interest. The basis of the present rejection is not the ability to deliver a polynucleotide to the genome of an animal, rather it is the failure of the specification to provide the necessary guidance for the appropriate promoters to affect the expression of any transgene in a manner which is the same as the endogenous promoter. Further, the specification fails to provide the necessary guidance to which transgenes should be delivered or how they should be expressed in order to mimic the specific neurological disease states set forth in the claims. Applicants have described generally a method of producing transgenic lines however, because of the unpredictability of transgene expression, the lack of examples or a description specific promoters, essentially all of the work required to define appropriate promoter elements

Art Unit: 1632

and transgenes, develop and optimize the conditions for *in vivo* expression has been left for others.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 and 32-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 1 and 32 are vague, unclear and indefinite in the recitation of “an expression pattern that is substantially the same” because the metes and bounds of ‘substantially’ is not clearly set forth. The difference in expression between the transgene and the endogenous gene which one would consider substantial is not specifically set forth, therefore the ability to determine if a particular transgenic animal met the limitations of the claims can not be determined. For example, it is unclear if one used a liver specific promoter, such as the albumin promoter that also has leaky expression in other tissues and cells, whether this expression pattern would meet the limitation of the claim. Though one may term the albumin promoter as liver specific pattern, clearly the expression pattern when used in the context of a transgene does not

Art Unit: 1632

produce the same expression pattern as the endogenous gene. Dependent claims 2-27 and 33-60 are included in the basis of the rejection because they fail to clarify the basis of the rejection listing only other potential pathways and general disorders for choosing a promoter without specifically indicating which promoter would meet the limitation of the claims.

Claim 7 and 38 are confusing in the recitation of "that is not operably linked to a coding sequence of said characterizing gene" because the limitations of independent claims 1 and 32 require that the transgene is not in the same location as the endogenous gene. Further, there is no limitations in claims 1 and 32 which indicate the presence of the characterizing gene, therefore specific recitation for the exclusion of this gene is unclear and confusing.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

a person shall be entitled to a patent unless -

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 2, 14, 18, 19, 22, 32, 33, 45, 49, 50, 53, 56 and 60 are rejected under 35 U.S.C. 102(e) as being anticipated by Leinwand *et al.* (US Patent 6,353,151B1, 1996).

Leinwand *et al.* teach a transgenic mouse model for congestive heart failure. Leinwand *et al.* teach that the transgene comprises heart tissue specific promoter, preferably the mouse or rat

Art Unit: 1632

myosin heavy chain promoter which operably linked to a polynucleotide which encodes a mammalian alpha myosin heavy chain protein (claim 1). In the instant case, though the promoters from the rat and mouse are derived from the myosin heavy chain gene, the promoters are considered different because they are derived from different genes from different species. Multiple lines are proposed and five independent lines of mice were reduced to practice and described (see Example 1). The promoters used by Leinwand *et al.* are considered tissue specific, however within the description of the lines generated, Leinwand *et al.* teach that the expression pattern varied from line to line (Example 2), and could also be detected in other tissues such as the uterus (column 18, lines 10-20). The use of various promoters and the use of various transgenes in the transgenic mouse models anticipates the collection of lines set forth in claims 1 and 2 because the promoter used is considered a tissue specific promoter, and in view of the indefiniteness of the term 'substantially' could fairly be interpreted to fall within the scope of the claims. The endogenous myosin heavy chain is expressed in the same tissues in several of the lines (claim 14), are functionally related (claim 18) and result in the disease state of congestive heart failure when expressed (claims 19 and 22). The methods disclosed to make the transgenic mice are conventional in the art comprising generating a transgene and using pronuclear injection to deliver the transgene (column 16, Example 1-claims 32 and 60). As noted above, the transgenes taught by Leinwand *et al.* anticipate the collection of lines, as a consequence the methods to make these lines are also anticipated (claims 33, 45, 49, 50, 53, 56).

Art Unit: 1632

Double Patenting

a rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

a statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-27 and 32-60 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-27 and 32-60 of co-pending Application No. 10/077,025. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. In the instant case the claims of each of the applications are duplicates of each other.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

Art Unit: 1632

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach


RAM R. SHUKLA, PH.D
PATENT EXAMINER